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Re: Comments on Draft Profile for Styrene

Dear Dr. Shane,

Thank you for providing me the opportunity to comment on the draft substance profile for styrene. For this review I focused only on the sections on *Experimental Animal Studies* and *Other Relevant Data*. If you wish to discuss anything in more detail, please do not hesitate to contact me. I can be reached at Redacted.

Sincerely yours,

*[original signed by Jean Rabovsky, Ph.D.
Toxicologist, Retired]*

COMMENTS ON THE NTP DRAFT STYRENE PROFILE

The profile is well written and succinctly synthesizes large amounts of information that allows the reader to understand the issues involved in understanding styrene carcinogenicity. A few comments are presented to provide some insight into the complexities of styrene carcinogenicity and its relationship to toxicity.

P.5. Experimental cancer studies with rats.

The conclusion that rat bioassay results are insufficient to reach a decision on carcinogenicity in this species is understandable given the inconsistent results. Closer attention, however, reveals differences among the studies that may preclude direct comparisons. Routes of exposure and doses varied. Complications due to styrene toxicity may also add to the difficulty of directly comparing all rat studies. Bioassays carried out at relatively high doses for long durations may have been partially responsible for the inconsistent results.

P.5, Other Relevant Data. CYP-dependent styrene metabolism

The discussion describes the role of cytochrome P450-dependent monooxygenase (CYP) activities in the metabolism of styrene to the putative carcinogen, styrene-7,8-oxide. While this enzyme class probably plays a major role in the conversion, porphyrin containing non-CYP enzymes may also play a role in the formation of styrene-7,8-oxide. Data suggesting a potential role for these non-CYP enzymes in styrene metabolism have been obtained from experiments in whole cells (Belvedere and Tursi, 1981; Belvedere et al., 1983) and cell-free systems (Ortiz de Montellano and Catalano, 1985; Geigert et al, 1986; Guengerich, 1990; Tuynman et al., 2000). The rates of the reactions may be less than the CYP-catalyzed reactions. However, under exposure conditions where styrene enters the systemic circulation prior to entering the liver, e.g., lung and blood, such non-CYP-dependent bioactivation reactions may have implications for styrene related carcinogenicity.

The Clara cell is hypothesized to be the major lung cell type to express CYP-dependent activity towards styrene. Relative rates notwithstanding, the alveolar type II cell also expresses CYP-dependent activity (Devereux et al., 1979; Rabovsky et al., 1989). Clara cells are located in the bronchiolar region of the lung whereas type II cells are located in the alveolar region of the lung. In the context of understanding styrene related lung tumors in mice, the results of Cruzan et al. (2001) are relevant because they show the alveolar type II cell is the predominant cell type in the lung tumors. Alveolar type II cells are multifunctional and provide the metabolic function in the alveolar region (Castranova et al., 1988). The relationship between Clara cell styrene metabolism and mouse lung tumors that contain alveolar type II cells has yet to be determined.

P.6, par.1 and p.7, par1. Relationship between styrene-induced lung toxicity and lung carcinogenicity.

In addition to a genotoxic mode-of-action for styrene related carcinogenicity, a possible separate role for styrene toxicity as a determinant has been suggested. This mode-of-action is considered to act through the CYP-dependent enzymes. Specifically, the toxic effect of the active metabolite, presumably styrene-7,8-oxide, leads to the formation of lung tumors in mice. Support for this hypothesis comes from the relationship between CYP-dependent metabolism in the bronchiolar Clara cells and styrene induced lung toxicity. However, according to Cruzan et al. (2001), the alveolar type II cell is the predominant cell type in the mouse styrene induced lung tumors. Hence the relationship between styrene induced bronchiolar toxicity and the induction of lung tumors in mice remains equivocal.

Conclusion

The profile on styrene is informative and adds to our knowledge about the effect of styrene on human health, in particular carcinogenicity. Apparent inconsistencies among some studies may be due to competing effects (e.g., carcinogenicity and non-cancer toxicity) and associated metabolic pathways and dose-response effects. Such difficulties, however, do not detract from the carcinogenicity classification of styrene. Rather they point out the need for additional studies into the modes-of-action of this chemical.

References

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